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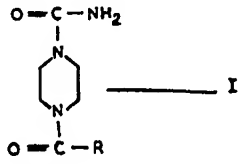
COMPLETE SPECIFICATION

Improvements relating to the preparation of New 1,4-Unsymmetrically Substituted Piperazines

We, AMERICAN CYANAMID COMPANY, a corporation organised under the laws of the State of Maine, United States of America, of 30, Rockefeller Plaza, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the preparation of new 1,4-unsymmetrically substituted piperazines.

The 1,4-unsymmetrically substituted piperazines of this invention may be illustrated by the following general formula:



wherein O=C–R is an acyl radical, R being an alkyl, aryl or halo-aryl radical, such as for example, benzoyl, dichlorobenzoyl, *o*-chlorobenzoyl, acetyl, propionyl, or n-butyryl.

The compounds of this invention are useful in the fields of chemistry, medicine and agriculture since they possess marked anticonvulsant activity and have demonstrated their ability to retard the progress of leukemia in the experimental mouse.

In accordance with the invention these compounds are prepared by treating 1-carbamyl-4-carbobenzoxy piperazine with hydrogen and a reducing catalyst to produce 1-carbamyl piperazine and then reacting this product with an acylating agent, i.e. an acyl halide or acyl anhydride.

In carrying out the invention the 1-carbamyl-4-carbobenzoxy piperazine, dissolved in a suitable neutral or weakly acidic solvent, is treated with hydrogen in the presence of palladium-charcoal catalyst to obtain an N-substituted piperazine. The carbamyl radical substituent on the N^1 or N^4 position (depending on the orientation selected) is non-functional and does not enter into the reaction.

Any suitable solvent may be used for the decarbobenzoxylation but a neutral or weakly acidic medium is preferred such as for example, water, absolute alcohol, acetic acid, or 50% aqueous alcohol. If an alkaline medium is used, the salt of 4-carbamyl-1-piperazinecarboxylic acid is obtained, which must then be acidified prior to isolation of the decarbobenzoxylated product.

The following examples are presented to illustrate the specific embodiments of this invention but are not intended to limit the scope thereof.

EXAMPLE I

A slurry of 65.8 gms. of 1-carbamyl-4-carbobenzoxy piperazine and 6.6 gms. of 10% palladium on charcoal in 500 ml. of water was refluxed and stirred while passing in hydrogen. When the reduction was complete (no further evolution of carbon dioxide) the mixture was filtered to give a clear solution of 1-carbamyl piperazine.

This solution was chilled to 5° C., and 35 grams of benzoyl chloride and 85 ml. of 4N sodium hydroxide solution were added simultaneously with vigorous stirring over the course of 30 minutes. The reaction mixture was adjusted to pH 12, warmed to 25° C., and then cooled to 5°C. At this point 7 gms. of a by-product melting at 156—173° C. was removed by filtration. The filtrate was concentrated to dryness under reduced pressure at 25° C., and the dry residue was extracted with hot absolute ethanol. The ethanolic extract was concentrated to give 44 gms. of colorless crystals of 1-benzoyl-4-carbamyl piperazine, m.p. 176—182° C. Recrystallization from water gave 27.2 gms. of colorless crystals melting at 187.0—187.5° C.

EXAMPLE II

To a solution of 33.1 gms. of 1-carbamyl

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piperazine in 200 ml. of 50% aqueous dioxane and 50 ml. of 4N aqueous sodium hydroxide solution, 41.8 gms. of 2,6-dichlorobenzoyl chloride and 50 ml. of 4N aqueous sodium hydroxide solution were added dropwise with cooling at such a rate that the pH of the mixture was maintained at 9—10. The colorless precipitate which formed was removed by filtration, washed with water, and dried. The yield of pure 1-(2,6-dichlorobenzoyl)-4-carbamyl piperazine was 52.6 gms. melting at 213—214° C.

Example III

A solution of 1-carbamylpiperazine was prepared as follows: To a solution of 41.3 gms. of 1-carbamyl piperazine hydrochloride, 41.8 ml. of 6N aqueous sodium hydroxide solution was added with cooling and stirring. The final pH was 12. The water was removed under reduced pressure at 20—25° C., leaving a partly crystalline residue which was slurried with 300 ml of glacial acetic acid and filtered to remove 9.2 gms. of sodium chloride crystals. The filtrate, containing 1-carbamylpiperazine, was chilled, and 28.2 gms. of acetic anhydride was added dropwise with stirring at 15° C. After removing an additional 3.7 gms. of sodium chloride crystals by filtration, the solvent was removed under reduced pressure leaving a crystalline residue. Recrystallization from a mixture of ethyl acetate and glacial acetic acid gave two crops of colorless crystals:

1st crop 24.8 gms. melting at 191—192° C.
2nd crop 12.6 gms. melting at 183—185° C.

Recrystallization of the first crop from isopropanol-water solution gave 20.4 gms. of colorless crystals of 1-acetyl-4-carbamyl piperazine, melting at 192.5—193° C.

Example IV

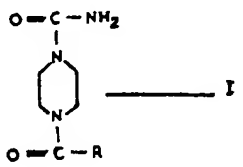
To a 100 ml. solution of 43 gms. of 1-carbamyl piperazine in dimethylformamide, 43.3 gms. of propionic anhydride was added while keeping the mixture cool by means of an ice bath. The reaction mixture was then allowed to come up to room temperature for several hours, after which time the mixture was chilled, and 52.5 gms. of crude product melting at 200—203° C. was removed by filtration. Recrystallization from absolute ethanol gave 39.4 gms. of 1-propionyl-4-carbamylpiperazine, m.p. 209—210° C.

Example V

To a solution of 33.1 gms. of 1-carbamyl piperazine hydrochloride in 200 ml. of 50% aqueous dioxane and 50 ml. of 4N aqueous sodium hydroxide solution, 35.0 gms. of *o*-chlorobenzoyl chloride and 50 ml. of 4N aqueous sodium hydroxide solution were added dropwise with cooling at such a rate that the pH of the mixture was maintained at 9—10. The colorless precipitate which formed was removed by filtration, washed with water, and dried. The yield was 46.5 gms. of product melting at 230—231° C. Recrystallization from methanol gave 33.9 gms. of colorless crystals of 1-(*o*-chlorobenzyl)-4-carbamylpiperazine, melting at 231—232° C.

What we claim is:

1. 1,4-Unsymmetrically substituted piperazines having the general formula:



wherein O=C–R is an acyl radical, R being an alkyl, aryl, or halo-aryl radical, such as, for example, benzoyl, dichlorobenzoyl, *o*-chlorobenzoyl, acetyl, propionyl, or *n*-butyryl.

2. The 1-aroyl-4-carbamyl piperazines.

3. The 1-lower-alkyl-carbonyl-4-carbamyl piperazines.

4. 1-benzoyl-4-carbamyl piperazine.

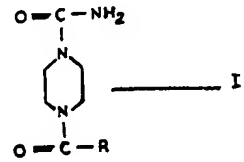
5. 1-(2,6 - dichlorobenzoyl) - 4 - carbamyl piperazine.

6. 1-acetyl-4-carbamyl piperazine.

7. 1-propionyl-4-carbamyl piperazine.

8. 1-(*o*-chlorobenzoyl)-4-carbamyl piperazine.

9. A method of preparing 1,4-unsymmetrically substituted piperazines having the formula:



wherein O=C–R is an acyl radical, R being an alkyl, aryl, or halo-aryl radical, such as, for example, benzoyl, dichlorobenzoyl, *o*-chlorobenzoyl, acetyl, propionyl or *n*-butyryl, which comprises treating 1-carbamyl-4-carbobenzoxy piperazine with hydrogen and a reducing catalyst, and then reacting 1-carbamyl piperazine thus produced with an acylating agent, i.e. an acyl halide or acyl anhydride.

10. A method according to claim 9, in which the reducing catalyst is palladium-charcoal.

11. A method according to claim 9 or 10, wherein 1-carbamyl piperazine is reacted with benzoyl chloride, 2,6-dichlorobenzoyl chloride, *o*-chlorobenzoyl chloride, acetic anhydride, propionic anhydride, or *n*-butyric anhydride.

12. A method of preparing 1,4-unsymmetrically substituted piperazines, having the formula I, substantially as hereinbefore described.

13. 1,4-unsymmetrically substituted piperazines whenever produced by the method according to any of claims 9—12.

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